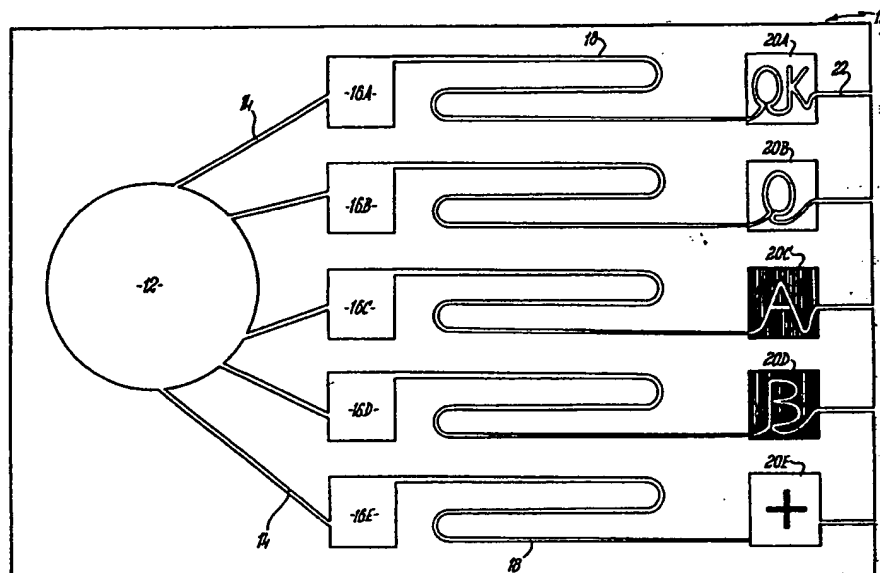




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : G01N 33/80, 33/48, 33/53 B01L 3/00	A1	(11) International Publication Number: WO 90/09596 (43) International Publication Date: 23 August 1990 (23.08.90)
(21) International Application Number: PCT/GB90/00202 (22) International Filing Date: 9 February 1990 (09.02.90) (30) Priority data: 8903046.4 10 February 1989 (10.02.89) GB (71)(72) Applicant and Inventor: VALE, David, Roger [GB/GB]; Hill Grove Cottage, Bretby, Burton-on-Trent, Stafford- shire DE15 0RD (GB). (74) Agent: DREVER, Ronald, Fergus; Swindell & Pearson, 48 Friar Gate, Derby DE1 1GY (GB). (81) Designated States: AT (European patent), AU, BE (Euro- pean patent), BR, CA, CH (European patent), DE (Euro- pean patent), DK (European patent), ES (European pa- tent), FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (Euro- pean patent), SE (European patent), SU, US.		Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the</i> <i>claims and to be republished in the event of the receipt of</i> <i>amendments.</i>

(54) Title: TESTING OF LIQUIDS



(57) Abstract

Apparatus (10) for testing blood comprising a single substantially rectangular transparent plastics moulding. The apparatus has a hollow (12) connected by five capillaries (14) to chambers (16A-E) each of which contains an impregnated permeable membrane. Further capillaries (18) lead from the chambers (16) decreasing in diameter along their length to respective indication chambers (20A-E). Each of the chambers (20) is such that, when blood passes thereinto either an indication thereon is obscured or an indication is provided on a previously plain background. Each of the chambers (20) is connected to atmosphere by vent capillaries (22).

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- 1 -

Testing of Liquids

This invention relates to apparatus for, and a method of testing liquids, particularly but not exclusively blood.

Many immunological tests are performed by determining antibody/antigen reaction by the presence of agglutination. The physical method of agglutination involves overcoming the zeta potential of particles (the natural repelling force) to make them adhere to each other and so form a mass of particles. To enable these particles to adhere to each other and overcome their natural repelling force it is necessary to either reduce their zeta potential or to physically bridge the gap between the particles. If this is achieved then agglutination occurs with the consequence that large agglutinates become visible to the naked eye. A widely known example of this is in determining blood groups where agglutination of red cells (haemagglutination) determines the presence of an antigen or antibody.

A red blood cell that carries the 'A' antigen will cause haemagglutination in the presence of 'A' antibody (Anti-A). This antibody which generally has five binding sites will cause haemagglutination by one site binding onto a red cell with the 'A' antigen and another site

binding with a similar adjacent red cell, the end result being bridges formed between masses of red cells to form an agglutinate clearly visible to the naked eye. The haemagglutination method has been and still is the only method used for determining blood groups. A certain combination of tests with Anti-A, Anti-B, Anti-AB and Anti-D will determine whether a blood sample is O, Rh positive etc. Blood grouping is not, of course, restricted to A,B,O and Rhesus, these being the most common determinations but can extend through the whole blood group system.

Most blood grouping requires a quite complex series of tests which already have been automated in many different forms - all of which detect the presence or absence of haemagglutination. For many years (at least 20) there has been a quick blood grouping system (Eldon cards) that have been used for confirmation grouping in the medical field as well as in education. Its principle is simple. Dried reagents are located on a card and a drop of blood is added to each reagent, this mixing causing the dried reagent to rehydrate and react with the red cells and agglutinate where appropriate; the pattern of agglutination determining the blood group. There is an increasing reluctance to use such an open system with the greater awareness of blood transmissible diseases.

Haemagglutination is not only restricted to blood groups but may be used in many serological tests. Hepatitis, syphilis and HIV (AIDS) tests may be performed using this method to determine the presence of the antibody to these diseases.

According to the present invention there is provided apparatus for testing for the presence of a substance in a liquid, the apparatus comprising means for locating a component which agglutinates with the substance or with the liquid when the substance is not present, means for supplying the liquid to the locating means to mix with the component, and passage means reaching from said locating means and including a restriction to flow whereby agglutinated material causes a reduction in flow of liquid through the passage means thereby providing a visual indication of the degree of agglutination.

The passage means may include a capillary tube along the whole length of which the mixture travels only in the absence of the agglutination.

The diameter of the capillary tube preferably decreases as it extends away from the locating means.

Desirably the capillary tube extends directly from the locating means to urge the liquid through the locating means by capillary action.

Alternatively or in addition the passage means includes a porous member with a pore size such that the mixture may only pass therethrough when substantially no agglutination occurs, and hence none of the substance is present.

The capillary or porous member may connect with an indicator chamber. The chamber may be constructed such that presence of the mixture therein makes a previously substantially invisible symbol visible. Alternatively the chamber may be constructed such that presence of the mixture therein makes a previously visible symbol substantially invisible.

The apparatus preferably comprises a plurality of locating means and passage means such that the presence of a plurality of substances can be simultaneously tested, each locating means including a different agglutinating component.

In such an apparatus each symbol is preferably different, and desirably one of the locating means and

respective passage means is a control such that no component, or a component which does not agglutinate with any substance in the liquid or the liquid itself, is used in the locating means.

The apparatus preferably comprises a collecting chamber connected to the or each locating means into which the liquid can be introduced. The collecting chamber and the or each locating means are preferably connected by a capillary tube such that the liquid is urged by capillary action in to the or each locating means.

If the apparatus is to be used for testing blood, the components are preferably monoclonal antibodies, to which an anti-coagulant may have been added.

The apparatus is preferably integrally formed and may be made of a transparent plastics material.

Also according to the present invention there is provided a method for testing for the presence of a substance in a liquid, the method comprising adding the liquid to a component which agglutinates with the substance or with the liquid in the absence of the substance, and passing the mixture through a restricted

passage means whereby the flow of liquid is controlled in accordance with the degree of agglutination to give an automatic visual indication determined by the presence or absence of liquid downstream of the restriction.

An embodiment of the present invention will now be described by way of example only with reference to the single figure of the accompanying drawings which shows a plan view of a blood testing apparatus.

The drawing shows an apparatus 10 suitable for testing blood to give an indication of blood type. The apparatus 10 comprises a single substantially rectangular transparent component, made, for example, by moulding a plastics material. The component 10 has a hollow 12 formed in the upper surface in use thereof, towards one of its ends. The hollow 12 is of a size to accept a drop of liquid. Within the component 10 leading from the hollow 12 towards the other end, are five capillaries 14, each 14 leading to a respective one of five chambers or locating means 16A, 16B, 16C, 16D, 16E.

Each chamber 16 contains a permeable membrane (not shown) which is impregnated with anti-coagulant. The membranes in chambers 16B, 16C, 16D, 16E are also impregnated respectively with monoclonal antibodies,

namely Anti-AB, Anti-A, Anti-B and Anti-D.

Further capillaries 18 lead from the downstream side of each of the chambers 16, to respective indication chambers 20A,B,C,D,E. The diameter of the capillaries 18 reduce as they extend from the chambers 16 and have the shape of a reverse squashed 'S'. Vent capillaries 22 lead from the opposite side of the chambers 20 and connect with atmosphere. The chambers 20 are constructed to either display an otherwise substantially invisible symbol, or to make an otherwise visible symbol substantially invisible, upon blood entering therein. The chamber 20A comprises a capillary arrangement shaped to form the symbol 'OK'. The chamber 20B includes an arrangement to provide the symbol 'O'. Chambers 20C and 20D have capillary arrangements to respectively show the symbols 'A' and 'B' and these are provided against a red background such that they are visible only if the capillary is empty. Chamber 20E has a red cross marked on it which is visible unless the chamber E is full of blood.

In use, a drop of blood is placed in the hollow 12. Capillary action causes blood from the hollow 12 to pass up the capillaries 14 into the chambers 16 to mix with the reagents impregnated in the membranes. The mixtures

thus formed are urged by capillary action along the capillaries 18. The converging of the capillaries 18 causes further mixing of the mixtures. If agglutination occurs in the mixture this will tend to block the respective capillary 18 and thus the flow of blood will not reach the respective chamber 20. If blood reaches the respective chamber 20 it either causes the message already thereon to be obscured, or causes a message to be visible thereon.

The chambers 16A and 20A and respective capillaries 14,18,22, act as a control, and blood should always flow into the chamber 20A making the symbol 'OK' visible and thus indicating that the apparatus 10 is functioning correctly. The chambers 16B and 20B and respective capillaries 14,18,22 indicate whether or not the blood group is O, i.e. if agglutination does not occur with Anti-AB then blood will flow in the capillary 18 leading to chamber 20B to highlight the 'O' symbol. The chambers 16C and 20C, and 16D and 20D, act in a similar manner respectively for blood groups A and B, but in these instances the A or B symbol is highlighted if agglutination does occur. Chambers 16E and 20E show whether the blood is positive and this symbol will remain visible if agglutination with Anti-D occurs.

There is thus described a relatively simple system for automatically providing a readily visible indication of blood type. The apparatus of the invention can be inexpensively manufactured due to its simplicity of construction. The system does not require significant handling of the blood being tested with the risks involved therewith.

Various modifications may be made without departing from the scope of the invention. for example it may not be necessary for the capillaries 18 to narrow. A membrane or other filter device which would block mixtures in which agglutination has occurred and allow free passage for other mixtures, could be used instead of or within the capillaries 18. Different methods could be used to illustrate whether agglutination has taken place.

A method of 'washing' a material, e.g. red blood cells, may be provided in which a reagent is passed through a permeable membrane which does not allow passage of the material, through the material into a reservoir. In the case of red blood cells saline solution may be passed through to remove serum previously added to the cells to allow passage of immunoglobulins as would be used in a Coombs test (Antiglobulin test).

Apparatus such as described can be used for many other medical tests. Obviously for such tests different relevant reagents will be provided in the chambers, and a different number of chambers may be required. This type of apparatus could be used for testing in the following fields.

- Rheumatoid Arthritis
- Pregnancy testing
- Glandular Fever
- Bacterial Identification
- S.L.E
- Hepatitis
- H.I.V.
- C.M.V.
- Thyroid Antibodies
- F.D.P.
- Antibody screening
- Direct antiglobulin testing

It would be possible to have more than one chamber containing reagents, whereby more than one reagent could be sequentially added. A network of branching could be used to facilitate various mixing alternatives. Further, a collecting chamber could be provided at the end of the system.

Claims:

1. Apparatus for testing for the presence of a substance in a liquid, the apparatus comprising means (16) for locating a component which agglutinates with the substance or with the liquid when the substance is not present, means (12,14) for supplying the liquid to the locating means (16) to mix with the component, characterised in that the apparatus also comprises passage means (18) reaching from said locating means (16) and including a restriction to flow whereby agglutinated material causes a reduction in flow of liquid through the passage means (18) thereby providing a visual indication of the degree of agglutination.

2. Apparatus according to claim 1, characterised in that the passage means (18) includes a capillary tube (18) along the whole length of which the mixture travels only in the absence of agglutination.

3. Apparatus according to claim 2, characterised in that the diameter of the capillary tube (18) decreases as it extends away from the locating means (16).

4. Apparatus according to claim 2 or claim 3, characterised in that the capillary tube (18) extends

directly from the locating means (16) to urge the liquid through the locating means (16) by capillary action.

5. Apparatus according to any of the preceding claims, characterised in that the passage means (18) includes a porous member with a pore size such that the mixture may only pass therethrough when substantially no agglutination occurs, and hence none of the substance is present.
6. Apparatus according to any of the preceding claims, characterised in that the passage means (18) connects with an indicator chamber (20).
7. Apparatus according to any of the preceding claims, characterised in that the apparatus comprises a plurality of locating means (16) and passage means (18) such that the presence of a plurality of substances can be simultaneously tested, each locating means (16) including a different agglutinating component.
8. Apparatus according to claim 7 when dependent on claim 6, characterised in that each passage means (18) connects with a different indicator chamber (20).
9. Apparatus according to claims 6 to 8 when dependent on claim 6, characterised in that the, or at least one of

the, indicator chambers (20) is constructed such that presence of the mixture therein makes a previously substantially invisible symbol visible.

10. Apparatus according to any of claims 6 to 9 when dependent on claim 6, characterised in that the, or at least one of the, indicator chambers (20) is constructed such that presence of the mixture therein makes a previously visible symbol substantially invisible.

11. Apparatus according to claim 9 or claim 10 when dependent on claim 8, characterised in that each symbol is different.

12. Apparatus according to any of claims 7 to 11 when dependent on claim 7, characterised in that one of the locating means (16) and respective passage means (18) is a control such that no component, or a component which does not agglutinate with any substance in the liquid or the liquid itself, is used in the locating means (16).

13. Apparatus according to any of the preceding claims, characterised in that the apparatus comprises a collecting chamber (12) connected to the or each locating means (16) into which the liquid can be introduced.

14. Apparatus according to claim 13, characterised in that the collecting chamber (12) and the or each locating means (16) are connected by a capillary tube (14) such that the liquid is urged by capillary action into the or each locating means (16).
15. Apparatus according to any of the preceding claims, characterised in that the component or at least one of the components is a monoclonal antibody.
16. Apparatus according to claim 15, characterised in that an anti-coagulant has been added to the or each component.
17. Apparatus according to any of the preceding claims, characterised in that the apparatus is integrally formed.
18. Apparatus according to any of the preceding claims, characterised in that the apparatus is made of a transparent plastics material.
19. A method for testing for the presence of a substance in a liquid, the method comprising adding the liquid to a component which agglutinates with the substance or with the liquid in the absence of the substance, characterised in that the mixture is passed through a restricted passage

means (18) whereby the flow of liquid is controlled in accordance with the degree of agglutination to give an automatic visual indication determined by the presence or absence of liquid downstream of the restriction.

20. A method according to claim 19, characterised in that the passage means (18) includes a capillary tube (18) along the whole length of which the mixture travels only in the absence of the agglutination.

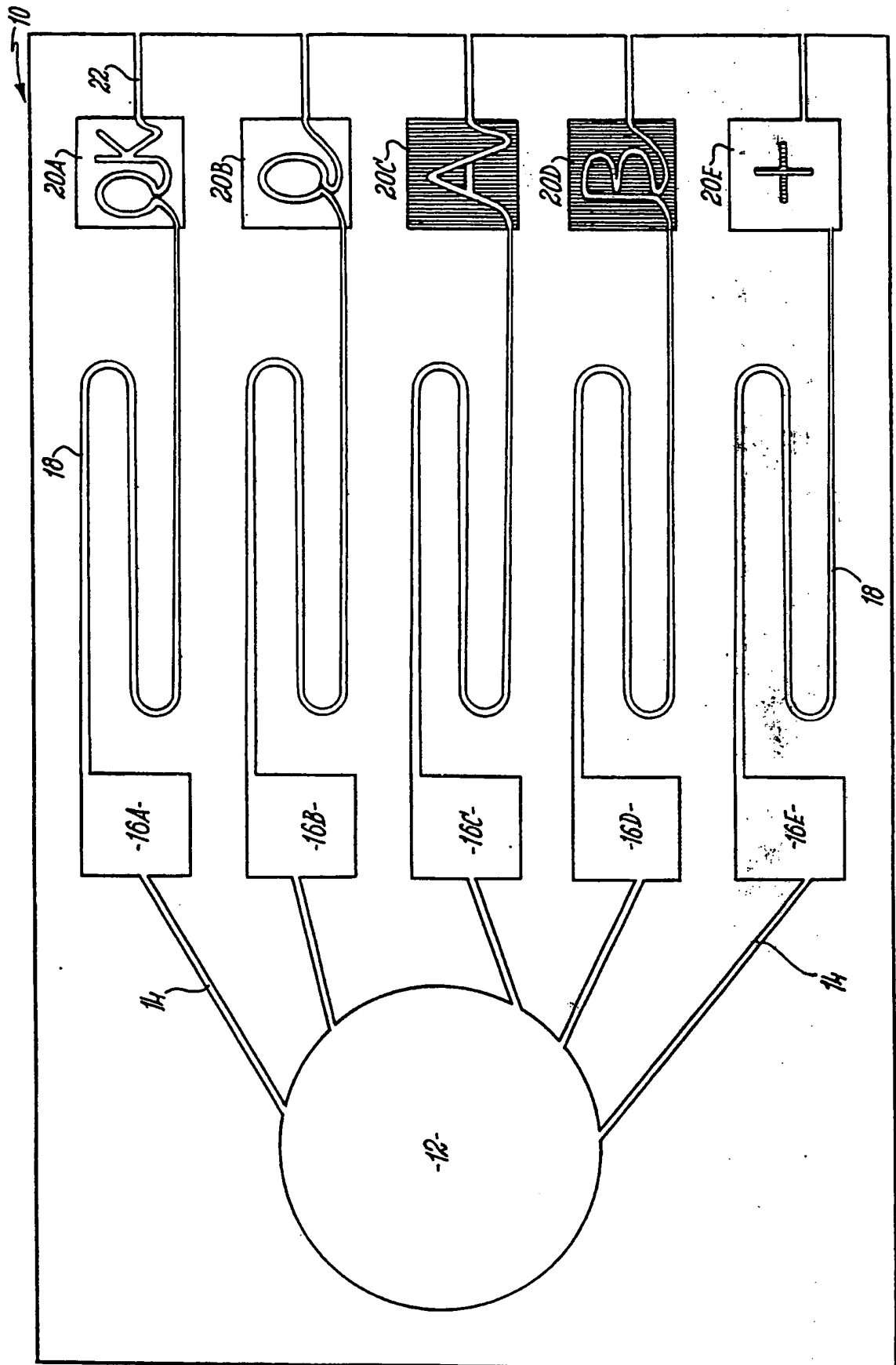
21. A method according to claim 19 or 20, characterised in that the liquid is simultaneously added to separate different components.

22. A method according to any of claims 19 to 21, characterised in that if agglutination does not occur upon adding the liquid to a component a previously substantially invisible symbol is made visible.

23. A method according to any of claims 19 to 22, characterised in that if agglutination does not occur upon adding the liquid to a component a previously visible symbol is made substantially invisible.

25. A method for testing blood characterised in that separate portions of the blood are combined with different

monoclonal antibodies and the mixtures formed are passed through a restricted passage (18) such that if agglutination occurs flow ceases in the passage and if no agglutination occurs either a previously invisible symbol is made visible or a previously visible symbol is made substantially invisible thereby indicating the blood type.



INTERNATIONAL SEARCH REPORT

International Application No. **PCT/GB 90/00202**

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁸ According to International Patent Classification (IPC) or to both National Classification and IPC IPC⁵: G 01 N 33/80, 33/48, 33/53, B 01 L 3/00		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System:	Classification Symbols	
IPC⁵	G 01 N	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁶		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	GB, A, 2197721 (H.V. COTTINGHAM) 25 May 1988 --	
A	EP, A, 0079861 (SOCIETE FINAMEX) 25 May 1983 --	
A	EP, A, 0104881 (ORTHO DIAGNOSTIC SYSTEMS INC.) 4 April 1984 --	
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P,A	EP, A, 0340562 (F. HOFFMANN-LA ROCHE AG) 8 November 1989 --	
P,A	EP, A, 0321736 (ABBOTT LABORATORIES) 28 June 1989 -----	
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>¹⁰ Special categories of cited documents: ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"A" document member of the same patent family</p> </div> </div>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search 8th May 1990		Date of Mailing of this International Search Report 12. 06. 90
International Searching Authority EUROPEAN PATENT OFFICE		Signature of Authorized Officer <div style="display: flex; align-items: center;"> <div style="margin-right: 20px;">M. Peis</div> <div style="border: 1px solid black; padding: 2px 5px;">M. PEIS</div> </div>

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

GB 9000202
SA 34160

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 30/05/90. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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